Project Overview

caBIG Adverse Event Reporting System (AERS)

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Document Control

Preparation

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Introduction

As part of the caBIG initiative, the Clinical Trials Management Systems (CTMS) Workspace participants have agreed that a 'componentized (modular) approach' would be employed in the development of informatics solutions to support clinical trials. The acquisition and reporting of Adverse Events (AEs) have been identified among the highest priorities.

This project overview is submitted by the City of Hope National Medical Center (COH) and outlines our proposal to develop an Adverse Events Reporting System (AERS). Our approach employs an iterative development approach based on Barry Boehm's spiral development model. Each phase of development activity includes an application evaluation period so that enhancements can be incorporated into subsequent builds. This approach is intended to deliver usable functionality in the shortest possible timeframe.

A graphic representation of the spiral model is included as Attachment A.

Statement of the Problem

The identification and monitoring of adverse events is essential for patient care evaluation and optimization. These issues are especially important for patients treated on clinical trials where treatment decisions are based on patient responses to therapeutic interventions and treatment-related toxicities.

Systems for the collection, evaluation, and reporting of AE's vary by institution. Most cancer centers and cooperative groups have databases that collect clinical trials data but not a system to aid in the assessment and reporting of toxicities. Government agencies have established automated mechanisms for collecting information of interest to them, but these systems are not integrated with each other or with local clinical trials databases. None of the current systems meets caBIG architecture and communication standards.

Important charateristics of a successful solution for adverse events data capture and reporting include:

- An open-source platform
- Direct data entry to capture information in a consistent way
- Integration with local systems to minimize redundant data entry and other operational inefficiencies.
- Conformance with HL-7 and Title 21 CFR Part 11 standards for electronic records and signatures
- A system development approach that identifies and satisfies the needs of the user community (including caBIG adopters, the AE Reporting Special Interest Group (SIG), and regulatory agencies)

This would yield an enhanced ability to collect, share, and analyze data across protocols and across organizations.

Definition of Terms

- **Module** – a unit of application functionality. Twelve modules have been identified for the AERS.
- **Spiral Model** – an incremental approach to the development of informatics solutions that involves iterative development to manage risks. User requirements are intentionally revisited and refined as part of each development phase.
- **Phase** – Each module will be developed and deployed in four phases, each of which has been defined as set of tasks within an iteration of the spiral model.
- **Statement of Work (SOW)** – A description of modules and phases to be developed as a caBIG project during a specified timeframe for a specified price. Each SOW may describe multiple modules and /or multiple phases within each module.

Project Scope

The envisioned AE reporting system will provide functionality to collect adverse event data, aiding in the assessment of grade and attribution and selection of proper identifying codes. Severe Adverse Events (SAEs) would be reported immediately to the Principal Investigator and other individuals key to the management of that trial AND assist in expediting reporting to the proper government agencies and to institutional monitoring boards.

In order to provide all the functionality required to meet everyone's need for adverse events data, twelve (12) separate modules have been identified. This breakdown was reviewed by the AE Reporting SIG and agreed upon.

Each module has distinct functionality although there are opportunities for grouping modules during the design and development process to enhance usability. Adopters can select to employ any or all modules as needed.

Module 1 - Adverse Event Data Capture

This module addresses the design and implementation of an application to capture Adverse Events when they occur. Based on information entered through a web interface, the system captures the severity of the adverse event and provides instructions for further reporting. Internal reporting capabilities allow the CRA to follow submissions, Quality Assurance to review them, and the Principal Investigator(s) to monitor toxicities and address further reporting requirements.

Module 2 – Interface Between AE Capture/Reporting Tool & Local CT Databases

Module 2 facilitates communication between the database created in Module 1 and the participating institution's clinical trials (CT) database. A pre-defined set of basic study participant demographics and protocol participation data elements is provided to the AERS via XML formatted output. In return, AE data that have been submitted on-line (to the AERS) is exported to the local database, thereby eliminating the need for duplicate entry.

Module 3 – Vocabulary Mapping Service

Module 3 will utilize the mappings created in the projects specified in our metadata related SOW, to allow generating customized reports and forms based on the preferences for vocabularies specified by the user. The vocabularies may also be determined by the external agency to which the data will be communicated in Module 4. The system will allow utilization of SNOMED CT, NCI Thesaurus, LOINC, HL7 RIM Vocabulary, ICD-9, ICD-O, and MedDRA. Other useful terminologies may be identified during the requirements phase for this module.

Module 4 – External Agency Reporting

Module 4 expands the functionality of Module 1 to electronically communicate SAEs to participating entities replacing systems such as AdEERS and CSAERS and providing generic alert messages to national cooperative groups and industrial sponsors (pharmaceuticals and other research organizations) where NCI funded protocols are involved.

NOTE: CDUS requires substantially more data than required for AEs and is not within the scope of this module.

Module 5 – Internal (institutional) Routing and Review

Module 5 provides a standardized electronic routing mechanism to alert institutional monitoring groups such as the Data Safety and Monitoring Board (DSMB) and Institutional Review Board (IRB) to adverse events.

Module 6 – Integrated Repository of AE Data

Module 6 establishes a data warehouse for evaluating adverse events across protocols. This repository sets the stage for later modules that provide information for data mining and public safety communications.

Module 7 – Acquisition of Lab Data to Quantitatively Identify Adverse Events

Module 7 will assist in the grading of quantitatively identified adverse events found in lab data acquired from local laboratory systems. Grading will be based on CTEP's CTC version 2.0 and CTCAE version 3.0.

Module 8 – Assistance in Grading Qualitative Adverse Events

Module 8 will provide assistance in the grading of adverse events found through clinical observation. Grading will be based on CTEP's CTC version 2.0 and CTCAE version 3.0.

Module 9 – Study Participant Self-Reporting of Adverse Events

Module 9 facilitates the reporting of adverse events by the study participant and their family caregivers. Data will be collected via web-entry or via a telephone.

Module 10 – Data Mining for Risk Patterns

Module 10 enables authorized individuals to gain access to the Adverse Events Data Warehouse for data mining across protocols. Information collected for the current CDUS system is also accessible. Statistical analysis of risk patterns should provide opportunities for improved clinical trials and knowledge acquisition.

Module 11 –Public Safety Website

Module 11 addresses dissemination of information about adverse events and drug and procedural safety alerts to the public. It uses the information collected in the data warehouse and evaluated via the functionality in module 10.

Module 12 – Automated Decision Support for Expectedness of AEs

This module refines the capture of adverse events data by providing protocol-specific information against which the event is compared. This enables the system to determine whether an adverse event is expected or unexpected at the initial point of entry.

Refer to Attachment B for a graphic representation of these 12 modules and their relationships.

Approach

The caBIG AERS, as proposed by COH, will be broken into 12 modules as described above. (The 12th module was added since presentation to the AE SIG. Each module will be developed through a series of 4 design and/or implementation phases illustrated by the spiral model in Attachment A. These phases are:

- business requirement
- logical design and first build
- physical design and second build
- final design and build

A separate statement of work (SOW) will be written to provide details of a logical segment of the AERS design and development. The SOW may address more than one module when requirements gathering and design strategies are more efficiently done together, and the resulting product will provide greater usability.

A requirements gathering and design phase will precede each implementation phase to establish a firm understanding of the needs of the user community and to clearly specify what will be developed. Business requirements will be gathered through interviews with clinical trial participants, sponsors, and government organizations. The information obtained during those interviews will be documented using a UML approach and then

shared with the CTMS workspace to discuss issues raised, and address process improvement opportunities. Once detailed design specifications are developed and reviewed, the SOW for the accompanying module development phase will be submitted.

During each phase, documents will be submitted to clearly outline progress and establish the next phase. On completion of each build, the application will be made available for use in order to evaluate the functionality and identify any needs that were missed or not previously identified. An iterative build process will ensure that these are all requirements are flushed out and incorporated.

Attachment C shows the development phases within the spiral model and a list of artifacts to be delivered upon completion of each phase.

We plan to begin by gathering the business requirements for Modules 1-4 in SOW1, with the rationale that the AE SIG has determined that the completion of these four modules will lead to practical, useful system functionality. Additional modules will be added in future SOWs to further enhance the AERS.

Attachment D illustrates our approach to handling the first 4 modules of the AERS using this phased approach. SOW1 covers the business requirements phase (phase 1) with overlaps in the timeline to ensure that discoveries affecting earlier modules are addressed. The anticipated start of the design and first build for these modules will be covered in future SOWs. (NOTE: The CTMS Metadata Mapping Project is SOW2.)

Assumptions and Risks

The following are general risks and assumptions made at the beginning of the AERS project. These will be expanded in subsequent SOWs.

- **Related to Sponsor and caBIG General**
  1. Assumptions will be made as to the start date of each SOW in developing the applicable project plan. The actual start dates, however, will be dependent upon the approval of the SOW.
  2. NCI's acceptance of an SOW indicates that the timeframes provided in the proposed project plan are considered reasonable and adequate. Contracts are fixed price.
  3. Design specifications will provide detailed report layouts and data exchange formats. Once approved, implementation will proceed as designed and can only be changed through design specifications in subsequent development iterations. Design creep would adversely affect the scope of each phase of development.
  4. The Common Terminology Criteria (CTC) will be the tool used for grading of AEs. The system to be developed will incorporate both CTCAE 3.0 and CTC version 2.0 to accommodate all open clinical trials.
  5. Unified Modeling Language (UML) standards will be employed for developing requirements and design artifacts.
  6. Parallel caBIG working groups may impact the scope of any phase of development or the implementation tools to be employed. These can only be addressed as they occur and may impact the scope of an SOW and/or the timeline.
  7. The AERS is intended to exchange data on NCI funded protocols and will not encompass trials conducted by other entities that do not use the CTC grading scale.

8. In the event that different views on issues, requirements, and subsequent designs result in an impasse regarding their resolution, the NCI shall have the final authority. The resolution of differences that require an inordinate amount of time may impact the established timeframe for an SOW.

- **Specific to COH**

9. Days off for COH team members (vacation, holiday, illness, etc) will be accounted for and adequately covered so that the project will proceed in a timely manner.
10. Major unexpected illness or other time off may, however, impact the timeline and will be addressed if they occur.
11. COH participation in, and knowledge of, activities in other caBIG workspaces, the HL7, and Title 21 CFR Part 11 are crucial to this project. Changes in those environments can impact the direction of this project and, if these should occur, it may be necessary to implement change orders to the project.

- **Specific to User Community**

12. Timely adopter and user community feedback throughout each phase and SOW of this project is critical to its success. It is expected that feedback from all participants will be received in a timely fashion.
13. Adopters will be expected to have basic computer skills, familiarity with a browser interface and an understanding of the standards established by caBIG.
14. Participants will need internet access and a valid email address for notification of artifact updates and to receive individualized questions.
15. In addition, COH will provide a web board mechanism for archiving of artifacts and updates as well as for the exchange of ideas within the user community. These will require a standard browser (Internet Explorer or Netscape) and familiarity with this technology. No training for use of these technologies will be provided to users.
16. Users, adopters and all involved entities will be forthcoming in identifying the requirements for the AERS and will respond in a timely fashion to requests for input.
17. Workspace participants will be able to respond to specifications and system reviews in a timely fashion commensurate with the schedule established in the SOW for that phase of development.
18. Representatives of the user groups identified will adequately understand their group's contribution to and expectations of the AE process. Information obtained from this group is critical and will be depended upon during development.
19. The system will ultimately provide information for import into local (institutional) databases through standard formats. This project has no provision to provide support to users to actually incorporate that data into the subject database.
20. FAQs will be provided for assistance in user orientation but no further training will be provided.

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Conclusion

This document provides an overview of the AERS project and City of Hope's planned approach. Information provided herein is general in nature as it addresses the entire project. SOWs may not be based on a single module or phase but rather on logical segments of work. Understanding of the 'big picture' is important to the understanding of future SOWs.

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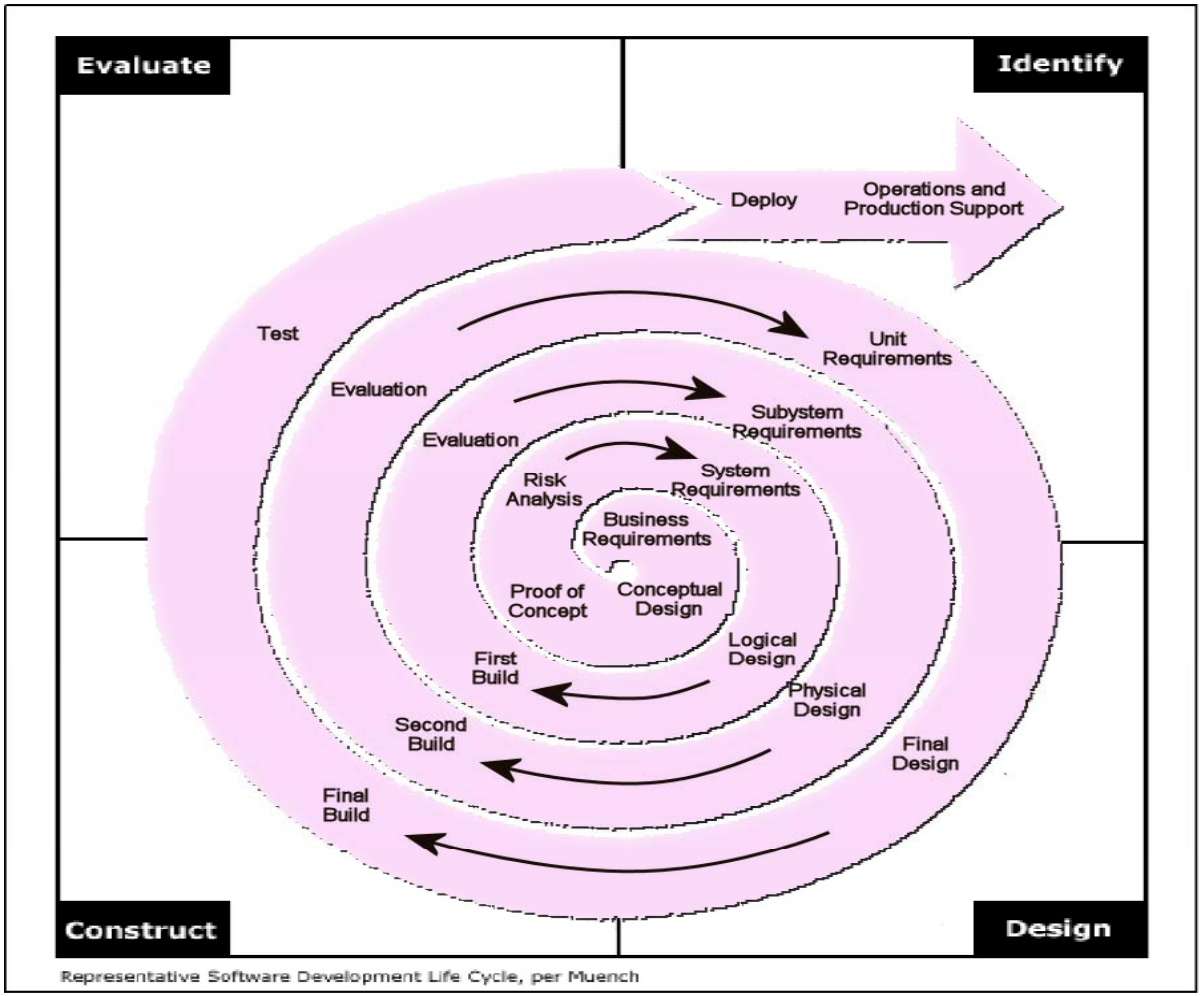
ATTACHMENT A



Representative Software Development Life Cycle, per Muench

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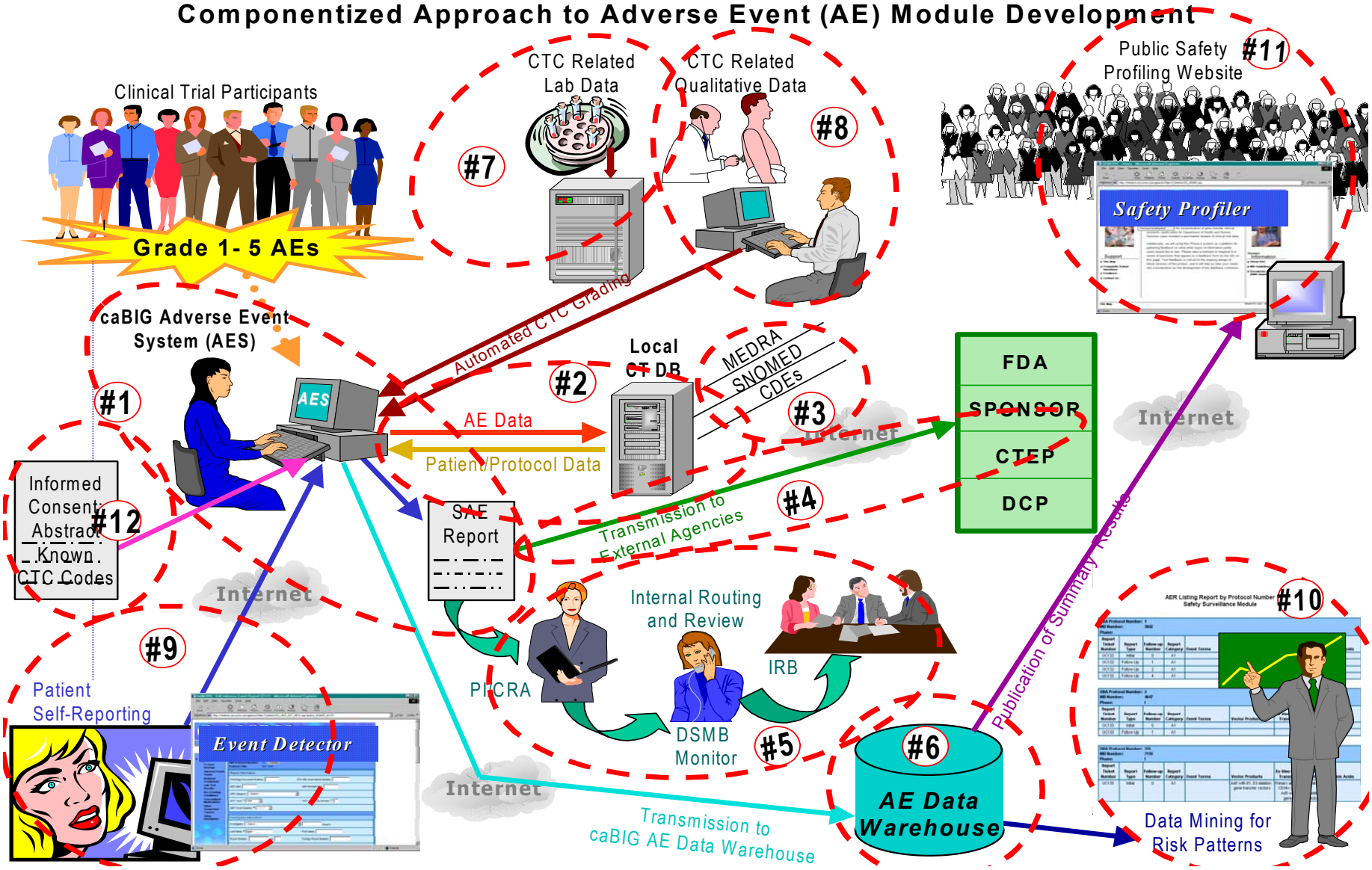
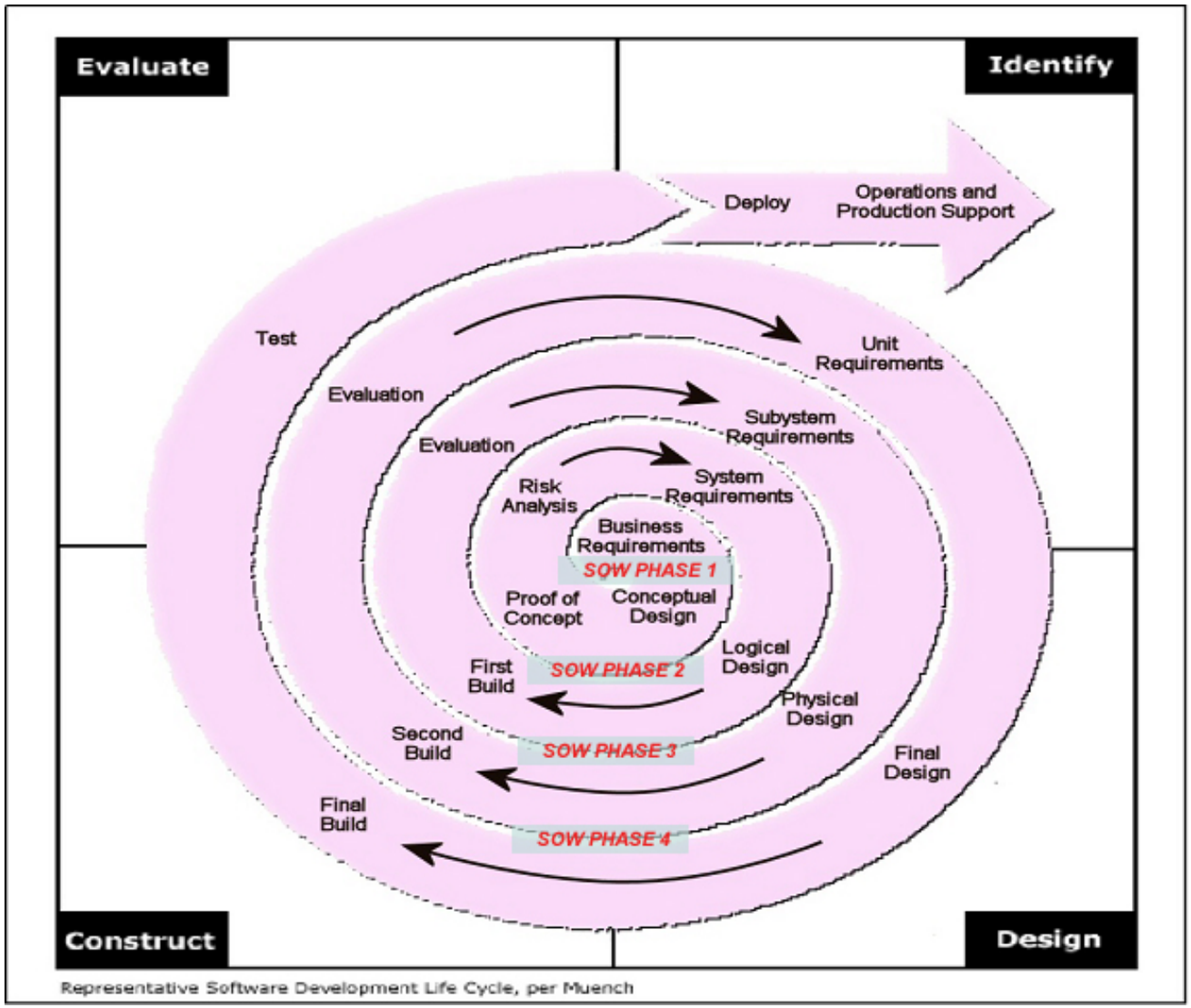
ATTACHMENT B

Componentized Approach to Adverse Event (AE) Module Development



ATTACHMENT C (page 1)



Representative Software Development Life Cycle, per Muench

ATTACHMENT C (page 2)

Template of Artifacts at each Phase				
	Business Reqts (Phase 1)	First Build (Phase 2)	Second Build (Phase 3)	Final Build (Phase 4)
Project Management Plan	**X**	**Updated project schedule**	**Updated project schedule**	**Updated project schedule**
Project Communication Plan	**X**	**Updated as needed**	**Updated as needed**	**Updated as needed**
Project Risk Matrix	**X**	**Updated as needed**	**Updated as needed**	**Updated as needed**
Staffing Plan	**X**	**Updated as needed**	**Updated as needed**	**Updated as needed**
Software Requirements Specification	**X**	**Updated**	**Updated as needed**	**Updated as needed**
Requirements Traceability Matrix	**X**	**Updated**	**Updated**	**Updated**
Requirements Peer Review Checklist	**X**	**Updated as needed**	**Updated as needed**	**Updated as needed**
Monthly Status Reports	**X**	**X**	**X**	**X**
Meeting Agenda & Notes/Action Items	**X**	**X**	**X**	**X**
Actions Log	**X**	**X**	**X**	**X**
Glossary of Terms	**X**	**Updated**	**Updated as needed**	**Updated as needed**
Data Definitions Document	**X**	**Updated**	**Updated as needed**	**Updated as needed**
Data Flow Scenario	**X**			
Activity/Sequence/Statechart/Class Diagrams	**X**			
Use Cases	**X**	**Updated**	**Updated**	**Updated**
Issues Log and Responses/Actions	**X**	**X**	**X**	**X**
Lessons Learned Document	**X**	**Updated as needed**	**Updated as needed**	**Updated as needed**

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ATTACHMENT D